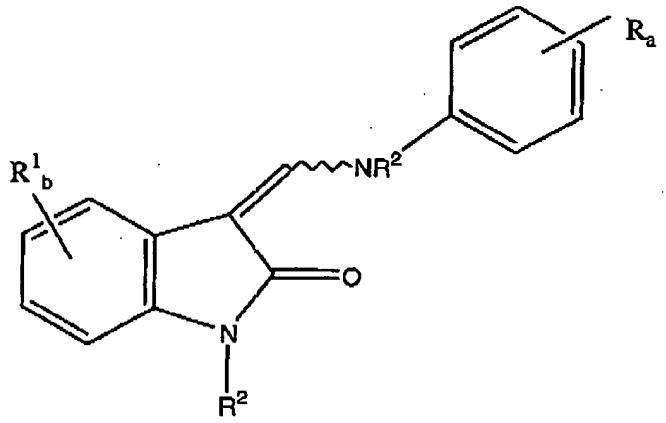
17465DIV(AP)
Serial No. 10/783,325
Filed: February 20, 2004

PATENT

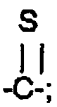
STATUS OF CLAIMS

1. (Currently Amended) A compound represented by the general formula I



wherein R^1 is selected from the group consisting of fluoro, chloro, ~~halogen, NO_2,~~ CN, C_1 to C_4 alkyl and aryl; R^2 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, $COCH_3$, CH_2CH_2OH, and $CH_2CH_2CH_2OH$ ~~and phenyl~~; R is selected from the group consisting of D, halogen, C_1 to C_8 alkyl, CF_3, OCF_3, OCF_2H, CH_2CN, CN, SR^2, $(CR_7R_8)_cC(O)OR^2$, $C(O)N(R^2)_2$, $(CR_7R_8)_cOR^2$, $HNC(O)R^2$, HN -$C(O)OR^2$, (C $R_7R_8)_cN(R^2)_2$, SO_2 $(CR_7R_8)_c$ $N(R^2)_2$, $OP(O)(OR^2)_2$, $OC(O)OR^2$, OCH_2O, HN-CH=CH, -$N(COR^2)CH_2CH_2$, HC=N-NH, N=CH-S, $(CR_7R_8)_c$-R^6 and $NR_2(CR^7R^8)_dR^6$ wherein R^6 is selected from the group consisting of halogen, dilower alkylamino, piperidinyl, 3-fluoropyrrolidinyl, 3-fluoropiperidinyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-pyrrolinyl, pyrrolidinyl, methyl isonipecotate, N-(2-methoxyethyl)-N-methylamyl , 1,2,3,6-tetrahydropyridinyl, morpholinyl, hexamethyleneiminyl, piperazinyl-2-one, piperazinyl, N-(2-methoxyethyl)ethylaminyl, thiomorpholinyl, heptamethyleneiminyl, 1-piperazinylcarboxaldehyde, 2,3,6,7-petrahydro-(1H)-1,4-diazepinyl-5(4H)-one, N-

methylhomopiperazinyl, (dimethylamino)pyrrolidinyl, N-(2-methoxyethyl)-N-propylaminyl, isoindolinyl, nipecotamidinyl, isonipecotamidinyl, 1-acetylpiperazinyl, 3-acetamidopyrrolidinyl, trans-decahydroisoquinolinyl, cis-decahydroisoquinolinyl, N-acetylhomopiperazinyl,
3-(diethylamino)pyrrolidinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-(2-methoxyethyl)-piperazinyl, 2-pyrrolidin-3-ylpyridinyl, 4-pyrrolidin-3-ylpyridinyl, 3-(methylsulfonyl)pyrrolidinyl, 3-picolylmethylaminyl, 2-(2-methylaminoethyl)pyridinyl, 1-(2-pyrimidyl)-piperazinyl,
1-(2-pyrazinyl)-piperazinyl, 2-methylaminomethyl-1,3-dioxolane,
2-(N-methyl-2-aminoethyl)-1,3-dioxolane, 3-(N-acetyl-N-methylamino)pyrrolidinyl, 2-methoxyethylaminyl, tetrahydrofurfurylaminyl, 4-aminotetrahydropyran, 2-amino-1-methoxybutane, 2-methoxyisopropylaminyl, 1-(3-aminopropyl)imidazole, histaminyl , N,N-diisopropylethylenediaminyl, 1-benzyl-3-aminopyrrolidyl 2-(aminomethyl)-5-methylpyrazinyl, 2,2-dimethyl-1,3-dioxolane-4-methanaminyl, (R)-3-amino-1-N-BOC-pyrrolidinyl, 4-Amino-1,2,2,6,6-pentamethylpiperidinyl, 4-aminomethyltetrahydropyran, ethanolamine and lower alkyl-substituted derivatives thereof and wherein when c is 1 said CH_2 may be



and $CH_2CH_2CH_2$; provided said alkyl or phenyl radicals may be substituted with one or two halo, hydroxy or lower alkyl amino radicals and wherein R^7 and R^8 are selected from the group consisting of H, F and C_1-C_4 alkyl or CR^7R^8 may represent a carbocyclic ring of from 3 to 6 carbons;
b is 0 or an integer of from 1 to 3;
a is 0 or an integer of from 1 to 5;
c is 0 or an integer of from 1 to 4;
d is an integer of from 1 to 5;

the wavy line represents a E or Z bond and pharmaceutically acceptable salts thereof; provided however said compound is not

3-Phenylaminomethylene-1,3-dihydro-indol-2-one,

3-[(3-Bromo-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(4-Bromo-phenylamino)-methyl]-1,3-dihydro-indol-2-one,

3-[(3-Bromo-phenylamino)-methyl]-1,3-dihydro-indol-2-one,

3-[(4-Ethyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-Ethyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(4-Methoxy-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

4-[(2-Oxo-1,3-dihydro-indol-3-ylididenemethyl)-amino]-benzoic acid ethyl ester,

3-[(2-Ethyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(3-Fluoro-4-methyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(3-Fluoro-2-methyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(4-Hydroxy-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(3-Chloro-4-hydroxy-phenylamino)-methylene]-1,3-dihydro-indol-2-one or

3-[(4-Fluoro-2-methyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one.

2. (Original) The compound of claim 1 wherein R^1 is selected from the group consisting of CH_3 , F and Cl.

3. (Original) The compound of claim 1 wherein a is 0.

4. (Original) The compound of claim 1 wherein R^2 is H.

5. (Original) The compound of claim 1 wherein R is selected from the group consisting of CH_3, CH_2CH_3, OCH_3, OH, t-butyl, F, CN, $C(O)NH_2$, N $C(O)CH_3$, $CH_2C(O)OH$, SO_2NH_2, $C(O)OH$, OCF_2H, isopropyl, C_2H_6OH, $C(O)OCH_3$, CH_2OH, NH-CH=CH, HC=N-N-H, N=CH-S, morpholinyl and $CH_2N(CH_3)_2$.

6. (Original) The compound of claim 3 wherein b is 0 and R^2 is H.

7. (Original) The compound of claim 4 wherein a is 1, R^2 is H and R is m-ethyl.

8. (Original) The compound of claim 4 wherein a is 1, and R is p-methoxy.

9. (Original) The compound of claim 4 wherein a is 1, and R is p-hydroxy.

10. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is m-hydroxy.

11. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-cyano.

12. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is m-$C(O)NH_2$.

13. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-$NC(O)CH_3$.

14. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-$CH_2C(O)OH$.

15. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-SO_2NH_2.

16. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-CH_2OH.

17. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is m-methoxy.

18. (Original) The compound of claim 4 wherein R is p-CH_2CH_2OH.

19. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is HN-CH=CH.

20. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is HC=N-NH.

21. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-N-morpholinyl.

22. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is N-CH-S.

23. (Original) The compound of claim 4 wherein a is 1, b is 0 and R is p-$OCHF_2$.

24. (Original) The compound of claim 4 wherein a is 2 and R is m-hydroxy and p-COOH.

25. (Original) The compound of claim 4 wherein a is 2 and R is m-hydroxy and p-CH_3.

26. (Original) The compound of claim 4 wherein a is 2 and R is m-hydroxy and p-OCH_3.

27. (Original) The compound of claim 4 wherein a is 2 and R is m-F and p-OCH_3.

28. (Original) The compound of claim 4 wherein b is 1 and R^1 is CH_3, a is 1 and R is m-hydroxy.

29. (Original) The compound of claim 4 wherein b is 1, R is CH_3, a is 1 and R is NH-N=CH.

30. (Original) The compound of claim 4 wherein b is 1, R is CH_3, a is 2 and R is N-CH=CH.

31. (Original) The compound of claim 4 wherein b is 1, R is CH_3, a is 1 and R is S-CH=N.

32. (Original) The compound of claim 4 wherein b is 1, R^1 is CH_3, a is 1 and R is p-hydroxy.

33. (Original) The compound of claim 4 wherein b is 1, R^1 is CH_3, a is 1 and R is p-CH_2OH.

34. (Original) The compound of claim 4 wherein b is 1, R^1 is CH_3, a is 2 and R is m-F and p-OCH_3.

35. (Original) The compound of claim 4 wherein b is 1, R^1 is Cl, a is 2 and R is m-hydroxy and p-OCH_3.

36. (Original) The compound of claim 4 wherein b is 1, R^1 is Cl, a is 2 and R is m, p-di-OCH_3.

37. (Original) The compound of claim 4 wherein b is 1, R^1 is Cl, a is 1 and R is HN-N=CH.

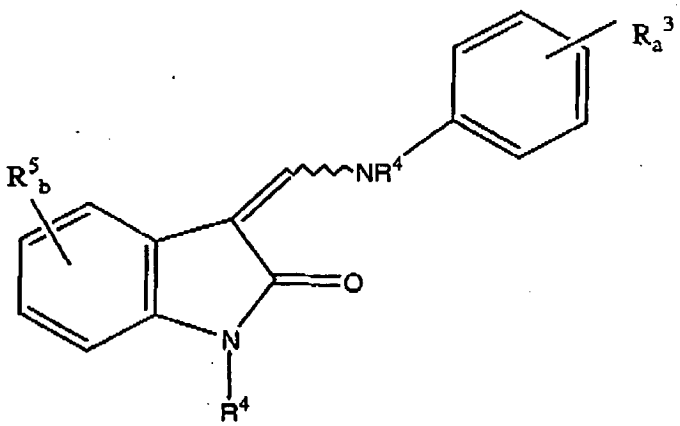
38. (Original) The compound of claim 4 wherein b is 1, R^1 is Cl, a is 1 and R is p-N-morpholinyl.

39. (Original) The compound of claim 4 wherein b is 1, R^1 is Cl, a is 2 and R is m-$CH_2N(C_2H_3)_2$ and p-hydroxy.

40. (Original) The compound of claim 4 wherein b is 1, R^1 is Cl, a is 1 and R is p-CH_2OH.

41. (Original) A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a compound according to Claim 1.

42. (Original) A compound represented by the general formula II:



wherein R^5 is selected from the group consisting of halogen, nitro, hydroxy, hydrocarbyl, substituted hydrocarbyl, amide, thioamide, amine, thioether and sulfonyl; R^3 is selected from the group consisting of D, halogen, nitro, hydroxy, hydrocarbyl, substituted hydrocarbyl, amide, thioamide, amine, thioether and sulfonyl and phosphonic acid; R^4 is selected from the group consisting of hydrogen, hydrocarbyl and substituted hydrocarbyl; b is 0 or an integer from 1 to 3; a is 0 or an integer of from 1 to 5; the wavy line represents a E or Z bond and pharmaceutically acceptable salts thereof provided however said compound is not

3-Phenylaminomethylene-1,3-dihydro-indol-2-one,

3-[(3-Bromo-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(4-Bromo-phenylamino)-methyl]-1,3-dihydro-indol-2-one,

3-[(3-Bromo-phenylamino)-methyl]-1,3-dihydro-indol-2-one,

3-[(4-Ethyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-Ethyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(4-Methoxy-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

4-[(2-Oxo-1,3-dihydro-indol-3-ylididenemethyl)-amino]-benzoic acid ethyl ester,

3-[(2-Ethyl-phenylamino)-methylene}-1,3-dihydro-indol-2-one,

3-[(3-Fluoro-4-methyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(3-Fluoro-2-methyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(4-Hydroxy-phenylamino)-methylene]-1,3-dihydro-indol-2-one,

3-[(3-Chloro-4-hydroxy-phenylamino)-methylene]-1,3-dihydro-indol-2-one or

3-[(4-Fluoro-2-methyl-phenylamino)-methylene]-1,3-dihydro-indol-2-one.

43. (Original) A method for treating diseases related to unregulated tyrosine kinase signal transduction, wherein said disease is selected from the group consisting of carcinoma, sarcoma, leukemia, erythromblastoma, glioblastoma, meningioma, astrocytoma, melanoma, myoblastoma, brain cancer, bladder cancer, ovarian cancer, gastric cancer, pancreas cancer, colon cancer, blood cancer, lung cancer, bone cancer, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, arthritis and restenosis, hepatic cirrhosis, atherosclerosis and surgical adhesions.glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies, psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative diseases the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

44. (Original) The method of claim 84 wherein said disease is diabetic retinopathy.

45. (Original) The method of claim 84 wherein said disease is age-related macular degeneration.

46. (Original) The method of claim 84 wherein said disease is psoriasis.

47. (Original) The compound of claim 1 wherein R is selected from the group consisting of fluoro, methyl, $NR_2(CR^7R^8)_dR^6$ and $(CR^7R^8)_c$-R^6, wherein R^6 is selected from the group consisting of diloweralkylamino, piperidinyl, 3-fluoropyrrolidinyl, 3-fluoropiperidinyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, piperdinyl 3-pyrrolinyl, pyrrolidinyl, methyl isonipecotate, N-(2-methoxyethyl)-N-methylamyl , 1,2,3,6-tetrahydropyridinyl, morpholinyl, hexamethyleneiminyl, piperazinyl-2-one, piperazinyl, N-(2-methoxyethyl)ethylaminyl, thiomorpholinyl, heptamethyleneiminyl, 1-piperazinylcarboxaldehyde, 2,3,6,7-tetrahydro-(1H)-1,4-diazepinyl-5(4H)-one, N-methylhomopiperazinyl, (dimethylamino)pyrrolidinyl, N-(2-methoxyethyl)-N-propylaminyl, Isoindolinyl, Nipecotamidinyl, isonipecotamidinyl, 1-acetylpiperazinyl, 3-acetamidopyrrolidinyl, trans-decahydroisoquinolinyl, cis-decahydroisoquinolinyl, N-acetylhomopiperazinyl,
3-(diethylamino)pyrrolidinyl, 1,4-dioxa-8-azaspiro[4.5]decaninyl, 1-(2-methoxyethyl)-piperazinyl, 2-pyrrolidin-3-ylpyridinyl, 4-pyrrolidin-3-ylpyridinyl, 3-(methylsulfonyl)pyrrolidinyl, 3-picolylmethylaminyl, 2-(2-methylaminoethyl)pyridinyl, 1-(2-pyrimidyl)-piperazinyl,
1-(2-pyrazinyl)-piperazinyl, 2-methylaminomethyl-1,3-dioxolane,
2-(N-methyl-2-aminoethyl)-1,3-dioxolane, 3-(N-acetyl-N-methylamino)pyrrolidinyl, 2-methoxyethylaminyl, tetrahydrofurfurylaminyl, 4-aminotetrahydropyran, 2-amino-1-methoxybutane, 2-methoxyisopropylaminyl, 1-(3-aminopropyl)imidazole, histamyl , N,N-diisopropylethylenediaminyl, 1-benzyl-3-aminopyrrolidyl 2-(aminomethyl)-5-methylpyrazinyl, 2,2-dimethyl-1,3-dioxolane-4-methanaminyl, (R)-3-amino-1-N-BOC-pyrrolidinyl, 4-amino-1,2,2,6,6-pentamethylpiperidinyl, 4-aminomethyltetrahydropyranyl, ethanolamine and alkyl-substituted derivatives thereof.

48. (Original) The compound of claim 47 wherein R^6 is selected from the group consisting of dimethylamino, diethylamino, 3-fluoropyrrolidinyl, 3-fluoropiperidinyl, 3-pyridinyl, 4-pyridinyl, pyrrolidinyl, morpholinyl, piperazinyl, heptamethyleneiminyl, tetrahydrofurfurylaminyl, 4-aminotetrahydropyranyl, N,N-diisopropylethylenediaminyl and 4-aminomethyltetrahydropyranyl.

49. (Original) The compound of claim 48 wherein R^6 is unsubstituted or mono or di-methyl substituted morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl.

50. (Original) The compound of claim 49 wherein R^6 is morpholinyl.

51. (Original) The method of claim 43 wherein R is selected from the group consisting of fluoro, methyl, $NR_2(CR^7R^8)_dR^6$ and $(CR^7R^8)_c$-R^6, wherein R^6 is selected from the group consisting of diloweralkylamino, 3-fluoropyrrolidinyl, piperidinyl, 3-fluoropiperidinyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-pyrrolinyl, pyrrolidinyl, methyl isonipecotate, N-(2-methoxyethyl)-N-methylamyl , 1,2,3,6-tetrahydropyridinyl, morpholinyl, hexamethyleneiminyl, piperazinyl-2-one, piperazinyl, N-(2-methoxyethyl)ethylaminyl, thiomorpholinyl, heptamethyleneiminyl, 1-piperazinylcarboxaldehyde, 2,3,6,7-tetrahydro-(1H)-1,4-diazepinyl-5(4H)-one, N-methylhomopiperazinyl, (dimethylamino)pyrrolidinyl, N-(2-methoxyethyl)-N-propylaminyl, isoindolinyl, nipecotamidinyl, isonipecotamidinyl, 1-acetylpiperazinyl, 3-acetamidopyrrolidinyl, trans-decahydroisoquinolinyl, cis-decahydroisoquinolinyl, N-acetylhomopiperazinyl,
3-(diethylamino)pyrrolidinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-(2-methoxyethyl)-piperazinyl, 2-pyrrolidin-3-ylpyridinyl, 4-pyrrolidin-3-ylpyridinyl, 3-(methylsulfonyl)pyrrolidinyl, 3-picolylmethylaminyl, 2-(2-methylaminoethyl)pyridinyl, 1-(2-pyrimidyl)-piperazinyl,

1-(2-pyrazinyl)-piperazinyl, 2-methylaminomethyl-1,3-dioxolane, 2-(N-methyl-2-aminoethyl)-1,3-dioxolane, 3-(N-acetyl-N-methylamino)pyrrolidinyl, 2-methoxyethylaminyl, tetrahydrofurfurylaminyl, 4-aminotetrahydropyran, 2-amino-1-methoxybutane, 2-methoxyisopropylaminyl, 1-(3-aminopropyl)imidazole, histaminyl , N,N-diisopropylethylenediaminyl, 1-benzyl-3-aminopyrrolidyl 2-(aminomethyl)-5-methylpyrazinyl, 2,2-dimethyl-1,3-dioxolane-4-methanaminyl, (R)-3-amino-1-N-BOC-pyrrolidinyl, 4-amino-1,2,2,6,6-pentamethylpiperidinyl, 4-aminomethyltetrahydropyranyl, ethanolamine and alkyl-substituted derivatives thereof.

52. (Original) The method of claim 51 wherein R^6 is selected from the group consisting of dimethylamino, diethylamino, 3-fluoropyrrolidinyl, 3-fluoropiperidinyl, 3-pyridinyl, 4-pyridinyl, pyrrolidinyl, morpholinyl, piperazinyl, heptamethyleneiminyl, tetrahydrofurfurylaminyl, 4-aminotetrahydropyranyl, N,N-diisopropylethylenediaminyl and 4-aminomethyltetrahydropyranyl.

53. (Original) The method of claim 52 where R^6 is unsubstituted or mono or di-methyl substituted morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl.

54. (Original) The method of claim 53 wherein R^6 is morpholinyl.